

# METANX<sup>®</sup> Tablets

**Metanx<sup>®</sup>** is an orally administered medical food for the dietary management of endothelial dysfunction in patients with diabetic peripheral neuropathy.

## DESCRIPTION

Each round coated purple colored tablet contains:

L-methylfolate Calcium (as Metafolin <sup>®</sup> )	3	mg
Pyridoxal-5'-Phosphate	35	mg
Methylcobalamin	2	mg

### Ingredients:

Dibasic Calcium Phosphate Dihydrate, Microcrystalline Cellulose 90, Microcrystalline Cellulose HD 90, Pyridoxal-5'-Phosphate, Opadry II Purple 40L10045 (Polydextrose, Titanium Dioxide, Hypromellose 3cP, Hypromellose 6cP, Glycerol Triacetate, Hypromellose 50cP, FD&C Blue #2, FD&C Red #40, Polyglycol 800), Microcrystalline Cellulose 50, Opadry II Clear Y-19-7483 (Hypromellose 6cP, Maltodextrin, Hypromellose 3cP, Polyglycol 400, Hypromellose 50cP), L-methylfolate Calcium, Magnesium Stearate, Methylcobalamin, and Carnauba Wax.

**Metanx<sup>®</sup>** tablets do not contain sugar, lactose, yeast or gluten.

## PHARMACOLOGY

*L-methylfolate* or *6(S)-5-methyltetrahydrofolate [6(S)-5-MTHF]*, is the primary biologically active diastereoisomer of folate<sup>1</sup> and the primary form of folate in circulation.<sup>2</sup> It is also the form which is transported across membranes into peripheral tissues,<sup>3</sup> particularly across the blood brain barrier.<sup>4</sup> In the cell, 6(S)-5-MTHF is used in the methylation of homocysteine to form methionine and tetrahydrofolate (THF).<sup>1</sup> THF is the immediate acceptor of one carbon units for the synthesis of thymidine-DNA, purines (RNA and DNA) and methionine.<sup>5</sup> About 70% of food folate and cellular folate is comprised of 6(S)-5-MTHF. Folic acid, the synthetic form of folate, must undergo enzymatic reduction by methylenetetrahydrofolate reductase (MTHFR) to become biologically active.<sup>6</sup> Genetic mutations of MTHFR result in a cell's inability to convert folic acid to 6(S)-5-MTHF.<sup>7</sup>

**Metafolin<sup>®</sup> (L-methylfolate calcium) is a substantially diastereoisomerically pure source of L-methylfolate containing not more than 1% D-methylfolate which results in not more than 0.03 milligrams of D-methylfolate in Metanx<sup>®</sup>.**

*D-methylfolate* or *6(R)-5-methyltetrahydrofolate [6(R)-5-MTHF]* is the other diastereoisomer of folate. Studies administering doses of 2.5 mg per day or higher resulted in plasma protein binding of D-methylfolate higher than L-methylfolate causing a significantly higher renal clearance of L-methylfolate when compared to D-methylfolate.<sup>8</sup> Further, D-methylfolate is found to be stored in tissues in the body, mainly in the liver. D-methylfolate is not metabolized by the body and has been hypothesized to inhibit regulatory enzymes related to folate and homocysteine metabolism and reduces the bioavailability of L-methylfolate.<sup>9</sup>

*Pyridoxal-5'-phosphate (PLP)* is the active form of vitamin B<sub>6</sub> and is used as the prosthetic group for many of the enzymes where this vitamin is involved. PLP is readily absorbed by the intestine by a process which is preceded by dephosphorylation to form pyridoxal. The phosphate group is regained during passage through the intestine. Pyridoxine, the parent compound of PLP and the most frequently used form of vitamin B<sub>6</sub>, requires reduction and phosphorylation before becoming biologically active. The PLP in Metanx<sup>®</sup> contains 25mg of pyridoxal (the active component of PLP).

*Methylcobalamin (Methyl-B<sub>12</sub>)* is one of the two forms of biologically active vitamin B<sub>12</sub>. Methyl-B<sub>12</sub> is the principal form of circulating vitamin B<sub>12</sub>, hence the form which is transported into peripheral tissue. Methyl-B<sub>12</sub> is absorbed by the intestine by a specific mechanism which uses the intrinsic factor and by a diffusion process in which approximately 1% of the ingested dose is absorbed. Cyanocobalamin and hydroxycobalamin are forms of the vitamin that require conversion to methylcobalamin.

## Pharmacokinetics:<sup>9,10</sup>

**Absorption and Elimination:** L-methylfolate is a water soluble molecule which is primarily excreted via the kidneys.<sup>10</sup> In a study of subjects with coronary artery disease (n=21), peak plasma levels were reached in 1-3 hours following ORAL/PARENTERAL administration.<sup>9</sup> Peak concentrations of L-methylfolate were found to be more than seven times higher than folic acid (129 ng ml<sup>-1</sup> vs. 14.1 ng ml<sup>-1</sup>) following ORAL/PARENTERAL administration. The mean elimination half-life is approximately 3 hours for L-methylfolate after the administration of 5mg of oral D,L-methylfolate. The mean values for C<sub>max</sub>, T<sub>max</sub>, and AUC<sub>0-12</sub> were 129 ng ml<sup>-1</sup>, 1.3 hr., and 383 respectively.

**Distribution:** Red blood cells (RBCs) appear to be the storage depot for folate, as RBC levels remain elevated for periods in excess of 40 days following discontinuation of supplementation.<sup>10</sup> Plasma protein binding studies showed that L-methylfolate is 56% bound to plasma proteins.<sup>9</sup>

## INDICATION AND USAGE

Metanx<sup>®</sup> tablets are indicated for the distinct nutritional requirements of patients with endothelial dysfunction<sup>11-13</sup> who present with loss of protective sensation<sup>14</sup> and neuropathic pain<sup>15-17</sup> associated with diabetic peripheral neuropathy.

Metanx<sup>®</sup> tablets are indicated for the distinct nutritional requirements of patients with endothelial dysfunction and/or hyperhomocysteinemia<sup>18</sup> who present with lower extremity ulceration(s).<sup>19-21</sup>

Metanx<sup>®</sup> should always be used under medical supervision.

## CONTRAINDICATIONS

There have been rare reports of hypersensitivity (allergic-like reactions) to **Metanx<sup>®</sup>**. Therefore, a known hypersensitivity to any of the components in the product is a contraindication to its use for any indication.

## PRECAUTIONS

### General:

Folic acid, when administered as a single agent in doses above 0.1mg daily, may obscure the detection of B<sub>12</sub> deficiency (specifically, the administration of folic acid may reverse the hematological manifestations of B<sub>12</sub> deficiency, including pernicious anemia, while not addressing the neurological manifestations). L-methylfolate may be less likely than folic acid to mask vitamin B<sub>12</sub> deficiency.<sup>22,23</sup> Folate therapy alone is inadequate for the treatment of a B<sub>12</sub> deficiency.

### Patient Information:

**Metanx<sup>®</sup>** is a medical food<sup>24</sup> to be used only under medical supervision.

## DRUG INTERACTIONS

**Metanx<sup>®</sup> added to other Drugs:** High dose folic acid may result in decreased serum levels for pyrimethamine and first-generation anticonvulsants (carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, valproic acid, valproate).<sup>25,26</sup> This may possibly reduce first generation anticonvulsants effectiveness and/or increase the frequency of seizures in susceptible patients.<sup>25,26</sup> While the concurrent use of folic acid and first generation anticonvulsants or pyrimethamine may result in decreased efficacy of anticonvulsants, no such decreased effectiveness has been reported with the use of L-methylfolate. Nevertheless, caution should be used when prescribing **Metanx<sup>®</sup>** among patients who are receiving treatment with first generation anticonvulsants or pyrimethamine. Pyridoxal 5'-phosphate should not be given to patients receiving the drug levodopa, because the action of levodopa is antagonized by pyridoxal 5'-phosphate. However, pyridoxal 5'-phosphate may be used concurrently in patients receiving a preparation containing both carbidopa and levodopa. Capecitabine (Xeloda<sup>®</sup>) toxicity may increase with the addition of leucovorin (5-formyltetrahydrofolate) (folate).

**Drugs added to Metanx<sup>®</sup>:** Antibiotics may alter the intestinal microflora and may decrease the absorption of methylcobalamin. Cholestyramine, colchicines or colestipol may decrease the enterohepatic re-absorption of methylcobalamin. Metformin, para-aminosalicylic acid and potassium chloride may decrease the absorption of methylcobalamin. Nitrous oxide can produce a functional methylcobalamin deficiency. Several drugs are associated with lowering serum folate levels or reducing the amount of active folate available. First generation anticonvulsants

(carbamazepine, fosphenytoin, phenytoin, phenobarbital, primidone, valproic acid, valproate)<sup>25,26</sup> and lamotrigine<sup>27</sup> (a second-generation anticonvulsant) may decrease folate plasma levels. Information on other second-generation anticonvulsants impact on folate levels is limited and cannot be ruled out. Diavalproex sodium,<sup>28</sup> topiramate,<sup>29</sup> gabapentin,<sup>30</sup> pregabalin,<sup>31</sup> levetiracetam,<sup>32</sup> tiagabine,<sup>33</sup> zonisamide,<sup>34</sup> have not reported the potential to lower folate in their respective prescribing information. Methotrexate, alcohol (in excess), sulfasalazine, cholestyramine, colchicine, colestipol, L-dopa, methylprednisone, NSAIDs (high dose), pancreatic enzymes (pancrelipase, pancratin), pentamidine, pyrimethamine, smoking, triamterene, and trimethoprim may decrease folate plasma levels. Warfarin can produce significant impairment in folate status after a 6-month therapy.

## ADVERSE REACTIONS

While allergic sensitization has been reported following both oral and parenteral administration of folic acid, allergic sensitization has not been reported with the use of Metafolin<sup>®</sup>. Paresthesia, somnolence, nausea and headaches have been reported with pyridoxal 5'-phosphate. Mild transient diarrhea, polycythemia vera, itching, transitory exanthema and the feeling of swelling of the entire body has been associated with methylcobalamin.

## DOSAGE AND ADMINISTRATION

The recommended dose is one tablet twice daily (B.I.D.) or as directed. Metanx<sup>®</sup> must be used under medical supervision.

## HOW SUPPLIED

Metanx<sup>®</sup> is available as a round coated purple colored tablet. Debossed with "PAL" on one side and "M" on the other. Commercial product is supplied in bottles of ninety (90) tablets or five hundred (500) tablets. Sample product is supplied in a bottle containing six (6) tablets.

Commercial Product (90 tablets)	0525-8019-90*
Commercial Product (500 tablets)	0525-8019-50*
Sample Product – Bottle (6 tablets)	0525-8019-06* Professional Samples – Not for sale.

\* PamLab, LLC does not represent this product code to be a National Drug Code (NDC) number. Instead, PamLab has assigned a product code formatted according to standard industry practice to meet the formatting requirements of pharmacy and health insurance computer systems.

## Storage:

Store at controlled room temperature 15°C to 30°C (59°F to 86°F) (See USP). Protect from light and moisture. Dispense commercial product (90 tablets) in original light-resistant container. Dispense sample product in original bottle.

## PATENTS

Some or all of the following patents may apply:

U.S. Patent No. 4,940,658	U.S. Patent No. 6,207,651
U.S. Patent No. 5,563,126	U.S. Patent No. 6,254,904
U.S. Patent No. 5,795,873	U.S. Patent No. 6,297,224
U.S. Patent No. 5,997,915	U.S. Patent No. 6,528,496
U.S. Patent No. 6,011,040	and other pending patent applications.

## REFERENCES

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- <sup>12</sup> van Etten R.W., deKoning E.J.P., Verhaar M.C., Gaillard A.J.M., Rabelink T.J. Impaired NO-dependent vasodilation in patients with Type II (non-insulin-dependent) diabetes mellitus is restored by acute administration of folate. *Diabetologia* 2002;45:1004-1010.
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<sup>24</sup>United States Food and Drug Administration Title 21 Code of federal Regulations 101.9(j)(8).

<sup>25</sup>PDR<sup>®</sup> For Nutritional Supplements, 2001;ISBN: 1-56363-364-7:157-167.

<sup>26</sup>Leucovorin Calcium (folinic acid) For Injection Prescribing Information:December 2003; Mayne Pharma (USA) Inc.

<sup>27</sup>Lamictal<sup>®</sup> (lamotrigine) Prescribing Information:August 2005; GlaxoSmithKline.

<sup>28</sup>Depakote<sup>®</sup> (divalproex sodium) Prescribing Information:January 2006; Abbott Laboratories.

<sup>29</sup>Topamax<sup>®</sup> (topiramate) Prescribing Information:June 2005; ORTHO-McNEIL NEUROLOGICS, INC.

<sup>30</sup>Neurontin<sup>®</sup> (gabapentin) Prescribing Information:December 2005; Parke-Davis.

<sup>31</sup>Lyrica<sup>®</sup> (pregabalin) Prescribing Information:March 2006; Parke-Davis.

<sup>32</sup>Keppra<sup>®</sup> (levetiracetam) Prescribing Information: March 2007; UCB, Inc.

<sup>33</sup>Gabitril (tiagabine) Prescribing Information: March 2005: Cephalon, Inc.

<sup>34</sup>Zonegran<sup>®</sup> (zonisamide) Prescribing Information: December 2004: Elan Pharma International Ltd.; licensed to Eisai Inc

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Revised 2/10